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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/536,087	03/24/2000	Michael J. Detmar	10287-051001	2190

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EXAMINER
DAVIS, NATALIE A

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 04/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/536,087	DETMAR ET AL.	
	Examiner	Art Unit	
	Natalie A. Davis	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,13-23 and 53-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6* is/are allowed.

6)☒ Claim(s) *1,7,13-23 and 53-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's traversal of the election of Group I, claims 1, 6-7, and 13-23 is acknowledged. The traversal is on the ground(s) that Groups I and V should be examined together because the inventions are drawn to treatment via administration of TSP-2 and the method steps are sufficiently related. This is not found persuasive for reasons indicated in the previous office action and because Group V is drawn to treatment of unwanted skin conditions, which are caused by various factors via modulation (increases and decreases) in TSP-2, whereas, Group I is only drawn to treatment of unwanted cell proliferation by increasing TSP-2 levels.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 6-7, and 13-23 are being examined as belonging to the elected Group I, while claims 2-5, 8-12, and 24-52 are withdrawn from examination as being drawn to a non-elected invention.

Applicant's amendment filed 16 January 2002 (Paper No: 9) is acknowledged. Accordingly, claims 1 and 6-7 are amended, claims 2-5, 8-12, and 24-52 are cancelled, and claims 53-74 are new. Claims 1, 6-7, 13-23, and 53-74 are pending.

Claim Objections

1. Claim 18 is objected to because of the following informalities: the claim recites " skin proliferation in the skin." This is redundant, as one would be able to determine that skin proliferation takes place in the skin. Appropriate correction is required. fixed

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 13-23, and 53-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

5. Claim 1 is drawn to a TSP-2 biologically active fragment. The specification discloses fragments of TSP-2 polypeptides as having at least 60-99% homology to SEQ ID NO: 2, which is at least 5 to 250 amino acids long and having at least 5 to 250 contiguous amino acids of SEQ ID NO: 2 (p. 18). There are many polypeptide fragments that may or may not perform the same biological functions and the specification does not give any guidance to which TSP-2 fragments, will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity and thus, must be preserved so the molecule will function as claimed, or how to make and select for such molecules. Thus, it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are broadly drawn to any TSP-2 biologically active fragment and applicant has not enabled all of these types of modifications because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed.

6. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular

Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all fragments with sequence similarity to the amino acid sequence shown in Fig. 1A (SEQ ID NO. 2). Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed. Accordingly, one of ordinary skill in the art would not know how to make or use the invention as claimed.

7. Claim 63 is drawn to a fragment comprising a procollagen domain or a functional fragment thereof. The specification discloses SEQ ID NO: 6-9 as derivatives of SEQ ID NO: 2, which comprise a procollagen domain (p 40). However, there is no teaching in the specification indicating how to make or select for functional fragments of a procollagen domain. There are many fragments that may be derived from SEQ ID NO: 6-9 (procollagen domain) that may or may not perform the same biological functions and the specification does not give any guidance to which procollagen domain fragments, will exhibit the biological activities as the claimed, or any guidance as to which regions of amino acid sequence are responsible for biological activity and thus, must be preserved so the molecule will function as claimed, or how to make and select for such molecules. Thus, it would be an undue burden to one of ordinary skill in the art to assay for claimed sequences, which are capable of functioning as contemplated. One cannot extrapolate the teachings of the specification to the breadth of the claims because the claims are

broadly drawn to any fragment comprising a procollagen domain or a functional fragment thereof and applicant has not enabled all of these types of modifications because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed.

8. Claims 1, 13-23, and 53-74 ~~are rejected~~ less than 35 U.S.C. 112, first paragraph. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Vas-Cath Inc. v. Mahurkar (CA FC) 19 USPQ2d 1111 (6/7/1991) clearly states that "written description" of invention required by first paragraph of 35 U.S.C. 112 is separate and distinct from that paragraph's requirement of enabling disclosure, since description must do more than merely provide explanation of how to "make and use" invention; applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed. An applicant shows possession by describing the claimed invention with all it limitations using such descriptive means as words, structures, diagrams, and formulas. Also, description of an actual reduction to practice, or by showing the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention at the time of filing.

9. The nature of the invention is to a method of treating a disorder by administering TSP-2 fragments. The specification discloses the injection of mice with clones overexpressing TSP-2 led to tumor growth inhibition, (p. 33-34), but does not disclose does not disclose any evidence regarding the treatment of unwanted cell proliferation by administering a biologically active fragment of TSP-2, SEQ ID NO: 2, 6-11, a functional fragment of a fragment comprising a procollagen domain,, or a type I repeat. Likewise, it does not disclose the isolation of and assaying of the claimed polypeptide fragments to determine if it possesses the same biological activity as TSP-2. In addition, no other examples are disclosed that conveys to one of skill in the art that the applicant was in possession of claimed fragments. There is no actual reduction to practice, sufficient descriptive information, such as definitive structural features, which are

critical to polypeptide activity, or complete detailed description of the function of claimed invention indicating that the claimed polypeptide fragments was indeed isolated, produced, and assayed for the uses disclosed. Thus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 6, 13-23, and 53-59, and 63-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Panetti, et al., (1997) in view of Volpert, et al., (1995), Ferrara, (1995), Laherty, et al., (1992), and LaBell, et al, (1992).

12. Panetti, et al. teach *in vitro* inhibition of cell proliferation by TSP-1 and -2 to, but does not teach administration of tsp-2. However, Volpert, et al, teach the inhibition of anigiogenesis by TSP-1 and -2 via administration in rat cornea. It would be obvious to administer TSP-2 to a subject to treat a disorder characterized by unwanted cell proliferation since Scalise, et al. that cell proliferation may be inhibited by TSP-2 and Volpert, et al. teach the inhibition of angiogenesis by the same via admisnistration. One would be motivated to combine the two teaching since Scalise, et al. teach cell proliferation is one component of angiogenesis (p. 209, col. 1) and Volpert, et al. teach in vivo methods. Furthermore, it would be obvious that VEGF would be inhibited since Ferrara teach VEGF inhibition in tumor growth suppression (abstract). In view of the above teaching, one would be motivated to use SEQ ID NO: 6-10 in the method as claimed since Laherty, et al., teach SEQ ID NO: 6-8 (Accession numbers: A42587 and A39851) and LaBell, et al. teach SEQ ID NO: 6 and 8-10 (Accession numbers: A47379 and A42173) because it is the same sequence and thus, will have the same function.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-5:30 (every other Friday off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa PhD can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis, PhD
March 25, 2002